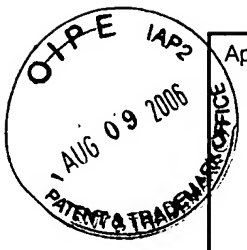

Application No. (if known): 10/595,932 Attorney Docket No.: 03818/0204413-US0

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(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Mladen Mercep et al.

Application No.: 10/595,932

Confirmation No.: 9163

Filed: May 19, 2006

Art Unit: N/A

For: 1-AZA-DIBENZO[E,H]AZULENES FOR THE TREATMENT OF CENTRAL NERVOUS SYSTEM DISEASES AND DISORDERS

Examiner: Not Yet Assigned

CLAIM FOR PRIORITY AND SUBMISSION OF DOCUMENTS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicant hereby claims priority under 35 U.S.C. 119 based on the following prior foreign application filed in the following foreign country on the date indicated:

Country	Application No.	Date
Croatia	P20030954A	November 21, 2003

In support of this claim, a certified copy of the said original foreign application is filed herewith.

Dated: August 9, 2006

Respectfully submitted,

Flynn H. Barrison
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By _____

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PCT/HR2004/000051

28 DEC 2004

(28 -12-.2004)

REPUBLIKA HRVATSKA
DRŽAVNI ZAVOD ZA INTELEKTUALNO VLASNIŠTVO

SVJEDODŽBA O PRAVU PRVENSTVA
PRIORITY CERTIFICATE

Državnom zavodu za intelektualno vlasništvo podnesena je prijava patenta s podacima kako slijedi:
The State Intellectual Property Office received the patent application containing the following indications:

(71) Ime(na) podnositelja prijave ili tvrtka i sjedište: / *Name(s) of applicants:*

Pliva-Istraživački institut d.o.o.
Prilaz Baruna Filipovića 29
10000 Zagreb, HR

(22) Datum podnošenja prijave patenta: / *Date(s) of filing of the application(s):* **21.11.2003.**

(21) Broj prijave patenta: / *Number(s) assigned to the application:* **P20030954A**

(54) Naziv izuma: / *Title of the invention:*

UPOTREBA 1-AZA-DIBENZO[e,h]AZULENA ZA PROIZVODNJU FARMACEUTSKIH PRIPRAVAKA ZA TRETIRANJE I PREVENCIJU BOLESTI I POREMEĆAJA SREDIŠNJEG ŽIVČANOG SUSTAVA

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REPUBLIKA HRVATSKA 2 DRŽAVNI ZAVOD ZA INTELEKTUALNO VLASNIŠTVO ZAGREB

RAVNATELJ
mr. sc. Željko Topić, dipl. oec.

U [illegible] 2004.

Kla[illegible]/I-9[illegible]/04-020/0051
Ur. [illegible]9-03[illegible]014

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

USE OF 1-AZA-DIBENZO[*e,h*]AZULENES FOR THE MANUFACTURE OF PHARMACEUTICAL FORMULATIONS FOR THE TREATMENT AND PREVENTION OF DISEASES AND DISORDERS OF THE CENTRAL NERVOUS SYSTEM

Disclosure of the Invention

The present invention relates to the use of compounds from the group of 1-aza-dibenzo[*e,h*]azulenes as well as of their pharmacologically acceptable salts and solvates for the manufacture of a pharmaceutical formulation for the treatment and prevention of diseases, damages and disorders of the central nervous system (CNS) caused by disorders of the neurochemical equilibrium of biogenic amines.

Prior Art

Irregularities in the steady state of biogenic amines (serotonin, norepinephrine, dopamine) and of other neurotransmitters and their receptors in CNS may be the cause of various mental diseases, damages and disorders (e.g. depression, schizophrenia, manic behavior and similar). Pathological changes in CNS caused by disorders of neurotransmitter concentration may occur due to an unbalanced (too big or too small) synthesis, irregularities in storing, releasing, metabolizing or reabsorption of a certain neurotransmitter.

The results of investigations directed to the understanding of pathogenesis of mental disorders have shown that a disorder in the serotonin equilibrium plays an important role in various diseases. The monoamine-deficiency hypothesis was one of the first explanations, wherein the symptoms of depression were connected to a reduction in the neurotransmission of monoamines, especially serotonin (5-HT) and noradrenaline, which was also confirmed by neurochemical tests as well as by a successful treatment

of the patients with substances increasing monoaminergic neurotransmission (*Expert Opin. Investig. Drugs* **2003**, 12, 531–543). In addition to the serotonergic and noradrenergic systems, a very important role in CNS function disorders is also played by the dopaminergic system. The understanding of the exact role and of the interactions of these neurotransmitter systems is made rather difficult by the great number of receptor subtypes and their pharmacological complexity. Thus, it has been observed that e.g. dopaminergic neurotransmission is regulated by 5-HT_{2A} receptors (L. G. Spampinato, *J. Neurochem.* **2000**, *74*, 693–701) and hence 5-HT_{2A} receptors may also be the target receptors in treating diseases and disorders, in whose pathology an important role is played by a disorder of the function of the dopaminergic system (psychoses and various addictions).

Pharmacological formulations are most frequently used in the treatment of pathological CNS disorders and a significant place among them as the most frequently applied medicines in the therapy of mental disorders is given to substances that, according to their structure, are polycyclic compounds (benzodiazepines, tricyclic and tetracyclic antidepressants, monoamino oxidase (MAO) inhibitors, selective inhibitors of serotonin reabsorption etc.).

A new area in pharmacotherapy was opened by introducing the novel tetracyclic antidepressant mianserin (Claghorn, J.; Lesem, M. D. *Prog. Drug Res.* **1996**, *46*, 243–262; Sperling, W.; Demling, J. *Drugs Today* **1997**, *33*, 95–102). Numerous tetracyclic derivatives showing pharmacological action in the treatment of the disorders of the neurochemical equilibrium in CNS are disclosed in the literature. WO 99/19317, WO 97/38991 and US 6,511,976 describe the manufacture of tetracyclic derivatives containing tetrahydrofuran ring and the use thereof as substances having antipsychotic, cardiovascular and gastrokinetic actions. US 4,145,434 discloses the manufacture of dibenzo(cyclohepta-, oxepino-, thiepino-)pyrrolidine and dibenzopyrrolidinoazepine derivatives as well as the use thereof as substances having a potential CNS action. The manufacture and an antidepressive action of some 1,2-

diazadibenzoazepines are disclosed in EP 0063525. The manufacture and a potential anxiolytic action of some tetracyclic isooxazolidine derivatives are disclosed as well (*Drugs Fut.* **2002**, 27, Suppl. A: C41; *Drugs Fut.* **2002**, 27, Suppl. A: P182, WO 96/14320, WO 96/14321). The introduction of a piperidine ring into a tetracyclic structure containing an oxepine ring resulted in the formation of the molecule Org-4428 showing an antidepressive action (Sperling, W.; Demling, J. *Drugs Today* **1997**, *33*, 95–102). The molecule Org-5222 contains a pyrrolidine ring fused to an oxepine nucleus and is described as a potential anxiolytic and antipsychotic (Sperling, W.; Demling, J. *Drugs Today* **1997**, *33*, 95–102). Some derivatives of 1,3-diaza-dibenzo[*e,h*]azulenes and salts thereof as a novel class of compounds with antiinflammatory action are known as well (US 3,711,489, US 4,198,421 and CA 967,573).

Derivatives of 1-thia-dibenzo[*e,h*]azulenes with aminoalkyloxy substituents on a thiophene ring and showing an antiinflammatory action were disclosed in WO 01/87890. From the class of 1-thia-dibenzoazulenes, in the literature there are disclosed derivatives substituted in 2-position by methyl, methyl ketone, nitro group or by derivatives of carboxy group (Cagniant PG, *C. R. Hebd. Sceances Acad. Sci.*, **1976**, *283*:683–686) and derivatives of 1-thia-dibenzoazulenes having aminoalkyloxy substituents in 2-position (WO 01/87890) as well as an antiinflammatory action thereof.

The preparation of 1-aza-dibenzo[*e,h*]azulenes, of their pharmaceutically acceptable salts and solvates as well as the antiinflammatory action thereof are disclosed in WO 03/097648.

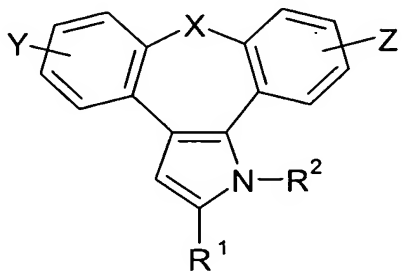
It has been surprisingly found that compounds from the class of 1-aza-dibenzo[*e,h*]azulenes substituted with an aminoalkylether chain are effective in the treatment of diseases and disorders of CNS. If compared with already known tetracyclic compounds acting upon CNS, the compounds of the present invention

consist of an unsaturated tetracyclic structure since they contain a pyrrole ring as the fourth ring, whereas the tetracyclic compounds acting upon CNS, which are disclosed in the literature, contain at least one saturated ring in their structure.

According to our knowledge, the use of 1-aza-dibenzo[*e,h*]azulenes and of their pharmaceutically acceptable salts and solvates for the manufacture of a pharmaceutical formulation for the treatment and prevention of diseases, damages and disorders of the central nervous system caused by disorders of neurochemical steady state has hitherto been neither disclosed nor suggested.

Solution to the Technical Problem

The present invention relates to the use of compounds from the class of 1-aza-dibenzo[*e,h*]azulenes of the general formula **I**



I

wherein

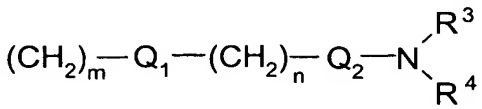
X means CH_2 or a heteroatom selected from the group O, S, S(=O), $S(=O)_2$, or NR^a, wherein R^a is hydrogen or a protecting group such as C_1-C_3-alkyl, C_1-C_3-alkanoyl, C_1-C_7-alkoxycarbonyl, C_7-C_{10}-arylalkyloxycarbonyl, C_6-C_{10}-aroyl, C_7-C_{10}-arylalkyl, trimethylsilyl or trimethylsilylethoxymethyl;

Y and Z independently from each other mean one or more identical or different substituents linked to any available carbon atom and may be halogen, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkinyl, halo-C_1-C_4-alkyl, hydroxy, C_1-C_4-alkoxy,

trifluoromethoxy, C_1-C_4-alkanoyl, amino, amino-C_1-C_4-alkyl, C_1-C_4-alkylamino, *N*-(C_1-C_4-alkyl)amino, *N,N*-di(C_1-C_4-alkyl)amino, thiol, C_1-C_4-alkylthio, sulfonyl, C_1-C_4-alkylsulfonyl, sulfinyl, C_1-C_4-alkylsulfinyl, carboxy, C_1-C_4-alkoxycarbonyl, cyano, nitro;

R^1 may be hydrogen, halogen, optionally substituted C_1-C_7-alkyl or C_2-C_7-alkenyl, C_2-C_7-alkinyl, optionally substituted aryl or heteroaryl and heterocycle, hydroxy, hydroxy-C_2-C_7-alkenyl, hydroxy-C_2-C_7-alkinyl, C_1-C_7-alkoxy, thiol, thio-C_2-C_7-alkenyl, thio-C_2-C_7-alkinyl, C_1-C_7-alkylthio, amino, *N*-(C_1-C_7-alkyl)amino, *N,N*-di(C_1-C_7-alkyl)amino, C_1-C_7-alkylamino, amino-C_2-C_7-alkenyl, amino-C_2-C_7-alkinyl, amino-C_1-C_7-alkoxy, C_1-C_7-alkanoyl, aroyl, oxo-C_1-C_7-alkyl, C_1-C_7-alkanoyloxy, carboxy, optionally substituted (C_1-C_7-alkyloxycarbonyl or aryloxycarbonyl), carbamoyl, *N*-(C_1-C_7-alkyl)carbamoyl, *N,N*-di(C_1-C_7-alkyl)carbamoyl, cyano, cyano-C_1-C_7-alkyl, sulfonyl, C_1-C_7-alkylsulfonyl, sulfinyl, C_1-C_7-alkylsulfinyl, nitro,

or a substituent represented with the formula **II**:



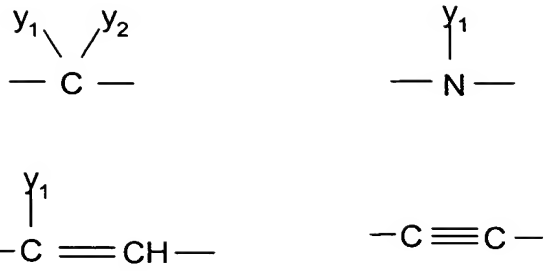
II

wherein

R^3 and R^4 simultaneously or independently from each other may be hydrogen, C_1-C_4-alkyl, aryl or together with N have the meaning of optionally substituted heterocycle or heteroaryl;

m and n have the meaning of an integer from 0 to 3;

Q_1 and Q_2 independently from each other have the meaning of oxygen, sulfur or a group:



wherein substituents

y_1 and y_2 independently from each other may be hydrogen, halogen, optionally substituted C_1-C_4-alkyl or aryl, hydroxy, C_1-C_4-alkoxy, C_1-C_4-alkanoyl, thiol, C_1-C_4-alkylthio, sulfonyl, C_1-C_4-alkylsulfonyl, sulfinyl, C_1-C_4-alkylsulfinyl, cyano, nitro, or together form a carbonyl or imino group;

R^2 has the meaning of hydrogen, optionally substituted (C_1-C_7-alkyl or aryl) or a protecting group: formyl, C_1-C_7-alkanoyl, C_1-C_7-alkoxycarbonyl, arylalkyloxycarbonyl, aroyl, arylalkyl, C_1-C_7-alkylsilyl;

of their pharmaceutically acceptable salts and solvates for the manufacture of pharmaceutical formulations for the treatment and prevention of diseases, damages and disorders of the central nervous system caused by disorders of neurochemical equilibrium of biogenic amines.

The compounds of the present invention are especially effective in treating those diseases and disorders where the neurochemical equilibrium of biogenic amines such as serotonin, norepinephrine and dopamine was disturbed and which may be caused by unbalanced (too big or too small) synthesis, irregularities in storing, releasing, metabolizing and/or reabsorption of a certain neurotransmitter.

It has been found that the compounds of the present invention exhibit a significant affinity for binding to serotonin receptors, especially to 5-HT_{2A} and 5-HT_{2C}. Preferably, the compounds of the present invention show affinity for binding to 5-

HT_{2A} and 5-HT_{2C} serotonin receptors in the concentration $IC_{50}<1\mu M$. Since serotonin receptors are crucial in pathophysiology of a series of CNS disorders (directly or indirectly by participating in the activation of some other neurotransmitter e.g. dopamine and/or receptor), the compounds of the present invention may be used for the manufacture of pharmaceutical formulations for the treatment and prevention of diseases, damages and disorders, wherein biogenic amines and their receptors play an important role.

In general, the compounds of the present invention may be used for the manufacture of pharmaceutical formulations that are used as antidepressants, anxiolytics, antipsychotics or as drugs for treating migraine.

Further, the compounds of the present invention may be used for the manufacture of pharmaceutical formulations for the treatment and prevention of diseases and disorders which are the result of disorders of neurochemical equilibrium in the central nervous system such as e.g. depression and modest depression, anxiety, bipolar disorders, sleeping disorders, sexual disorders, psychoses, borderline psychoses, schizophrenia, migraine, personality disorders and obsessive-compulsive disorders, social phobias or panic attacks, organic mental disorders in children, aggression, memory disorders and personality disorders in elderly people, addiction, obesity, bulimia and similar disorders, snoring, premenstrual troubles.

Likewise, these compounds may be used in the treatment and/or prevention of CNS damage caused by trauma, brain stroke, neurodegenerative diseases, cardiovascular disorders such as high blood pressure, thrombosis, infarct and similar diseases as well as in gastrointestinal disorders.

The effective dose of the active substance of the present invention and of a pharmaceutically acceptable salt or solvate thereof depends on the efficacy of the compound of the general formula **I**, on the nature and the severity of the disease and

the disorder of CNS as well as on the body weight of the patient treated and may be from 0.001–10 mg/kg body weight. In any case a unit dose for an adult of an average weight of 70 kg is understood to be 0.07–1000 mg of the compound of the general formula **I** or of a pharmaceutically acceptable salt or solvate thereof. A unit dose may be administered once or several times daily, e.g. 2, 3 or 4 times daily, most frequently 1 to 3 times daily.

The present invention more specifically relates to an effective dose of the compounds which bind to serotonin, sigma, adrenergic, dopamine or muscarinic receptors and/or act as inhibitors of reabsorption of one or more biogenic amines (serotonin, dopamine, norepinephrine).

Pharmaceutically acceptable salts relate to salts of hydrobromic, hydrochloric, perchloric, sulfuric, maleic, fumaric, tartaric, citronic, benzoic, mandelic, methanesulfonic, benzenesulfonic, oxalic, p-toluenesulfonic, 2-naphthalenesulfonic, phosphoric acids. Pharmaceutical solvates relate to hydrates, ethanolates and similar.

Further, the present invention relates to a pharmaceutical formulation containing an effective non-toxic dose of the compounds of the present invention as well as pharmaceutically acceptable carriers or solvents.

The pharmaceutical formulations are obtained by blending a therapeutically active amount of a certain substance as the active ingredient with a pharmaceutically acceptable carrier, which may have different forms depending on the desired administration route. These pharmaceutical formulations especially relate to oral, sublingual, rectal, percutaneous or parenteral administration route.

Pharmaceutical formulations may be manufactured using conventional pharmaceutical auxiliaries and manufacture routes. Forms for oral administration may be syrups, capsules, tablets and similar forms where usual solid carriers are inert substances such

as lactose, starch, glucose, methylcellulose, magnesium stearate, dicalcium phosphate, mannitol and similar, and usual liquid oral auxiliaries include ethanol, glycerol, water and similar. All auxiliaries may be optionally blended with disintegrants, diluents, granulating agents, wetting agents, binders and similar by using conventional methods. Parenteral forms may be manufactured by using water or some other sterile carrier. When for the manufacture of oral formulations some of the common liquid carriers e.g. water, glycol, oils, alcohols and similar are used, the formulation may be in the form of syrup, emulsion, soft gelatine capsules or sterile injectable liquids e.g. ampoules, or of non-aqueous liquid suspensions. When for the manufacture of oral formulations a solid carrier such as starch, sugar, kaolin, wetting agents, binders, disintegrants and similar is used, the formulation may be in the form of a powder, capsule, tablet, hard gelatine capsules or granules that may be administered in capsules, and the amount of the solid carrier may vary (most frequently from 1 mg to 1 g). Due to their easy use, tablets and capsules are the most convenient oral formulations wherein a solid carrier is used. For parenteral formulations the carrier is mostly sterile water, though other ingredients may be contained therein as well in order to improve solubility. For the manufacture of injectable solutions, sodium chloride solution, glucose solution or a mixture thereof is used. Injectable solutions may also contain a component for a delayed release of active component. Convenient oils that may be used for this purpose are e.g. arachic oil, sesame oil, cottonseed oil, corn oil, soybean oil, synthetic glycerol esters of long-chain fatty acids or a mixture of some of said oils. Injectable suspensions may be manufactured in such a way that a suitable liquid carrier used is blended with a suspending agent. In formulations convenient for percutaneous administration, as a carrier there is understood a substance improving the penetration of the active substance and/or a suitable wetting agent, which may be combined with a suitable additive of any provenience, which additives do not cause harmful effects on skin. Said additives may facilitate the skin administration and/or may be used in the manufacture of the desired formulations, which may be applied in various ways e.g. transdermally, spot-on, or in the form of an ointment.

To improve the solubility and/or stability of the present compounds, in pharmacological formulations there may be used α-, β- or γ-cyclodextrins or derivatives thereof, especially hydroxyalkyl substituted cyclodextrins i.e. 2-hydroxypropyl-β-cyclodextrin. Cosolvents such as e.g. alcohols may also improve the solubility and/or stability of the present compounds in various pharmaceutical formulations.

The effect of the compounds of the present invention on the neurochemical steady state was determined by *in vitro* investigations such as a radionuclide-marked radioligand binding assay for 5-HT_{2A} (Bonhaus D.W. Br. *J. Pharmacol.* **1995**, *115*:622; Saucier C. *J. Neurochem.* **1997,** *68*:1998) and 5-HT_{2C} receptors (Wolf W.A. *J. Neurochem.* **1997**, *69*:1449) and by *in vivo* investigations in a tail suspension test (Vogel H.G. and Vogel W.H. Drug Discovery and Evaluation Pharmacological Assays, Springer **1997,** 304), in a forced swim test in mice (Porsolt R.D. et al. *Arch. Int. Pharmacodyn.* **1977**, *229*:327–336), in meta-chlorophenyl piperazine (m-CPP) test on rats (*Drug Dev. Res.* **1989**, *18*:119–144), and in apomorphine, tryptamine, norepinephrine (ATN) test in rats (*Arch. Int. Pharmacodyn.* **1977**, *227*:238–253).

In *vitro* method for determining affinity for binding to 5-HT_{2A} and 5-HT_{2C} receptors

A small concentration of a radioligand having a great affinity for binding to a receptor was incubated with a tissue sample enriched with a certain receptor (1–5 mg of tissue) in a buffered medium (0.2–5 mL). Recombinant human HT_{2A} and HT_{2C} receptors were expressed in CHO-K1 or COS-7 cells and were also used for competitive binding. During incubation the radioligand bound to the receptor. When a binding balance was achieved, the receptors to which the radioligand was bound were separated from those to which said ligand was not bound, and the radioactivity of the receptor/radioligand complex was measured. The interaction of the tested compounds

with receptors was tested in competitive binding experiments. Various concentrations of tested compounds were added to the incubation mixture containing a prepared tissue enriched with corresponding receptors and the radioligand. The radioligand binding was inhibited by the test compounds proportionally to the affinity of a certain compound for the receptor and to the concentration of the compound.

The radioligand used for the determination of binding to 5-HT_{2A} receptor was [^{3}H]-ketanserin and the tissue used was human cortex or recombinant 5-HT_{2A} receptor expressed in CHO-K1.

The radioligand used for the determination of binding to 5-HT_{2C} receptor was [^{3}H]-mesulergine and the tissue used was choroid plexus or recombinant 5-HT_{2C} receptor expressed in CHO-K1 cells.

Compounds showing IC_{50} in concentrations lower than 1 μM, were considered to be active.

Forced swim test in mice

Male CD1 mice of the weight of 20–25 g were used for the experiment. On the day of the experiment the animals were placed into a glass cylinder (height 18.2 cm, diameter 13.3 cm) filled with water warmed to 22 °C to the height of 10 cm. The immobility defined as the end of the struggling of the animal and the beginning of floating, wherein the movements were reduced to those indispensable for the animal to keep its head over the water surface, started to be recorded after two minutes and then it was monitored during 4 minutes. The tested substance was administered *per os* 30 minutes before the test.

The percentage of animals showing a passive behaviour was calculated and compared with a control group treated with a carrier. The compounds that in a dose of 10 mg/kg

reduced the immobility of animals for 30 % and more over the control group were considered to be active.

Tail suspension test in mice

Male Balb/cJ mice of the weight of 20–25 g were used for the experiment. Mice were suspended from their tails at a height of about 90 cm and were observed for 5 minutes. The mice hanging fully motionless for 1 minute during the observation period were defined as depressive. In animals treated with a substance having an antidepressive action the period of immobility was shortened.

The percentage of animals showing a passive behaviour was calculated and compared with a control group treated with a carrier. The compounds that in a dose of 10 mg/kg reduced the immobility of animals for 40 % and more over a control group were considered to be active.

Meta-chlorophenyl piperazine (m-CPP) test on rats

The tested substance was administered to rats *per os* 1 hour before the test and m-CPP in a dose of 1 mg/kg was administered intravenously 15 minutes before the test. At the beginning of the experiment the treated animals were subjected to an open field test on rats (*Drug Dev. Res.* **1989**, 18, 119–144): the apparatus consisted of an open box having the dimensions 80 × 65 × 35 cm, which in one wall had an opening with a diameter of 10 cm, by which it was connected to a non-illuminated compartment having the dimensions 25 × 21 × 21 cm, and the opening was illuminated by a light source (IR source or Kleverlux®; 12 V/20 W) from the distance of 66 cm; one hour after administering the tested substance, the animals were placed in the dark (non-illuminated) compartment so that their heads were turned away from the illuminated exit and the passing of the animals from the dark compartment to the bright one was measured for 10 minutes.

As an active dose of the substance there was defined a dose at which the effect induced by m-CPP was reduced for 40 % and more.

Apomorphine, tryptamine, norepinephrine (ATN) test in rats

At the beginning of the experiment (t = 0) the animals were injected intravenously by 1.25 mg/kg of apomorphine, then by 40 mg/kg of tryptamine (t = 60 minutes) and by 1.25 mg/kg of norepinephrine (t = 90 minutes).

There were watched a state of exceptional agitation and normal behaviour during 60 minutes (apomorphine test), then bilateral clonic convulsions of back paws and a general tremor of the body in tryptamine test (observation period 5 minutes) and lethality during 120 minutes after the injection in norepinephrine test.

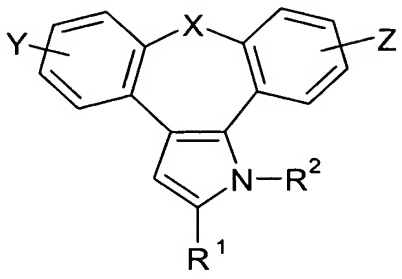
The percentage of animals showing a passive behaviour was calculated and compared with a control group treated with a carrier.

The compounds which in a dose of 10 mg/kg reduced the period of duration of observed effects (mobility) for 40 % over a control group were considered to be active in *in vivo* testings.

Some of the present compounds tested in the above assays showed an action in at least two of said tests, though these results represent only an illustration of the biological action of the compounds and do not limit the present invention in any way.

CLAIMS

1. Use of the compounds of the general formula **I**



I

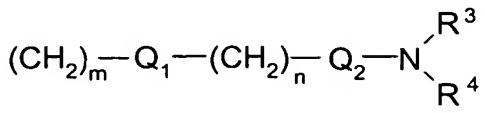
wherein

X means CH_2 or a heteroatom selected from the group O, S, S(=O), $S(=O)_2$, or NR^a wherein R^a is hydrogen or a protecting group such as C_1-C_3-alkyl, C_1-C_3-alkanoyl, C_1-C_7-alkoxycarbonyl, C_7-C_{10}-arylalkyloxycarbonyl, C_6-C_{10}-aroyl, C_7-C_{10}-arylalkyl, trimethylsilyl or trimethylsilylethoxymethyl;

Y and Z independently from each other mean one or more identical or different substituents linked to any available carbon atom and may be halogen, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkinyl, halo-C_1-C_4-alkyl, hydroxy, C_1-C_4-alkoxy, trifluoromethoxy, C_1-C_4-alkanoyl, amino, amino-C_1-C_4-alkyl, C_1-C_4-alkylamino, *N*-(C_1-C_4-alkyl)amino, *N,N*-di(C_1-C_4-alkyl)amino, thiol, C_1-C_4-alkylthio, sulfonyl, C_1-C_4-alkylsulfonyl, sulfinyl, C_1-C_4-alkylsulfinyl, carboxy, C_1-C_4-alkoxycarbonyl, cyano, nitro;

R^1 may be hydrogen, halogen, optionally substituted C_1-C_7-alkyl or C_2-C_7-alkenyl, C_2-C_7-alkinyl, optionally substituted aryl or heteroaryl and heterocycle, hydroxy, hydroxy-C_2-C_7-alkenyl, hydroxy-C_2-C_7-alkinyl, C_1-C_7-alkoxy, thiol, thio-C_2-C_7-alkenyl, thio-C_2-C_7-alkinyl, C_1-C_7-alkylthio, amino, *N*-(C_1-C_7-alkyl)amino, *N,N*-di(C_1-C_7-alkyl)amino, C_1-C_7-alkylamino, amino-C_2-C_7-alkenyl, amino-C_2-C_7-alkinyl, amino-C_1-C_7-alkoxy, C_1-C_7-alkanoyl, aroyl, oxo-C_1-C_7-alkyl, C_1-C_7-alkanoyloxy, carboxy, optionally substituted (C_1-C_7-

alkyloxycarbonyl or aryloxycarbonyl), carbamoyl, *N*-(C_1-C_7-alkyl)carbamoyl, *N,N*-di(C_1-C_7-alkyl)carbamoyl, cyano, cyano-C_1-C_7-alkyl, sulfonyl, C_1-C_7-alkylsulfonyl, sulfinyl, C_1-C_7-alkylsulfinyl, nitro,
or a substituent represented with the formula **II**:



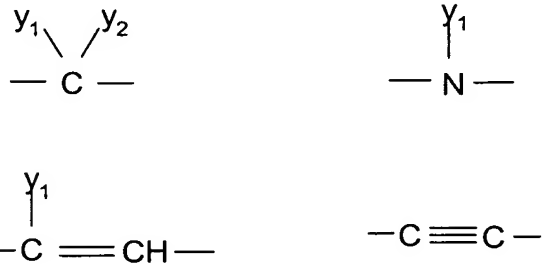
II

wherein

R^3 and R^4 simultaneously or independently from each other may be hydrogen, C_1-C_4-alkyl, aryl or together with N have the meaning of optionally substituted heterocycle or heteroaryl;

m and n have the meaning of an integer from 0 to 3;

Q_1 and Q_2 independently from each other have the meaning of oxygen, sulfur or a group:



wherein substituents

y_1 and y_2 independently from each other may be hydrogen, halogen, optionally substituted C_1-C_4-alkyl or aryl, hydroxy, C_1-C_4-alkoxy, C_1-C_4-alkanoyl, thiol, C_1-C_4-alkylthio, sulfonyl, C_1-C_4-alkylsulfonyl, sulfinyl, C_1-C_4-alkylsulfinyl, cyano, nitro, or together form a carbonyl or imino group;

R^2 has the meaning of hydrogen, optionally substituted (C_1-C_7-alkyl or aryl) or a protecting group: formyl, C_1-C_7-alkanoyl, C_1-C_7-alkoxycarbonyl, arylalkyloxycarbonyl, aroyl, arylalkyl, C_1-C_7-alkylsilyl;

and of their pharmaceutically acceptable salts and solvates for the manufacture of pharmaceutical formulations for the treatment and prevention of diseases, damages and disorders of the central nervous system caused by disorders of neurochemical equilibrium of biogenic amines.

2. Use according to claim 1, wherein the selected biogenic amines are serotonin, norepinephrine and dopamine.

3. Use according to claim 1, wherein the compounds of the general formula **I** act upon the neurochemical equilibrium by regulating the synthesis, storing, releasing, metabolizing and/or reabsorption of biogenic amines.

4. Use according to claim 3, wherein the compounds of the general formula **I** have an affinity for binding to a receptor of one or more biogenic amines.

5. Use according to claim 4, wherein the compounds of the general formula **I** have a significant affinity for binding to serotonin 5-HT_{2A} and 5-HT_{2C} receptors.

6. Use according to claim 5, wherein the compounds of the general formula **I** have an affinity for binding to selected serotonin receptors in a concentration of IC50<1μM.

7. Use according to claim 1, wherein the diseases and disorders of the central nervous system are selected from the group consisting of anxiety, depression and modest depression, bipolar disorders, sleeping disorders, sexual disorders, psychosis, borderline psychosis, schizophrenia, migraine, personality disorders and obsessive-

compulsive disorders, social phobia or panic attacks, organic mental disorders in children, aggression, memory disorders and personality disorders in elderly people, addiction, obesity, bulimia and similar disorders, snoring, premenstrual troubles.

8. Use according to claim 1, wherein the damages of the central nervous system are caused by trauma, brain stroke, neurodegenerative diseases, cardiovascular disorders such as high blood pressure, thrombosis, infarct as well as by gastrointestinal disorders.

9. Use according to claim 1, wherein the compounds of the general formula **I**, pharmaceutically acceptable salts and solvates thereof are selected from the group consisting of:

1H-8-oxa-1-aza-dibenzo[e,h]azulene;

*11-chloro-1*H-*8-oxa-1-aza-dibenzo*[e,h]*azulene;*

*1*H-*8-thia-1-aza-dibenzo*[e,h]*azulene*;

1H-8-oxa-1-aza-dibenzo[e,h]azulene-2-carbaldehyde;

11-chloro-1H-8-oxa-1-aza-dibenzo[e,h]azulene-2-carbaldehyde;

*1*H-*8-thia-1-aza-dibenzo*[e,h]*azulene-2-carbaldehyde;*

*1-(2-trimethylsilyl-ethoxymethyl)-1*H-*8-oxa-1-aza-dibenzo*[e,h]*azulene-2-carbaldehyde*;

*11-chloro-1-(2-trimethylsilyl-ethoxymethyl)-1*H-*8-oxa-1-aza-dibenzo*[e,h]*azulene-2-carbaldehyde;*

*1-(2-trimethylsilyl-ethoxymethyl)-1*H-*8-thia-1-aza-dibenzo*[e,h]*azulene-2-carbaldehyde;*

*[1-(2-trimethylsilyl-ethoxymethyl)-1*H-*8-oxa-1-aza-dibenzo*[e,h]*azulen-2-yl]-methanol*;

*[11-chloro-1-(2-trimethylsilyl-ethoxymethyl)-1*H-*8-oxa-1-aza-dibenzo*[e,h]*azulen-2-yl]-methanol*;

*[1-(2-trimethylsilyl-ethoxymethyl)-1*H-*8-thia-1-aza-dibenzo*[e,h]*azulen-2-yl]-methanol*;

*dimethyl-{2-[1-(2-trimethylsilyl-ethoxymethyl)-1*H*-8-oxa-1-aza-dibenzo*[e,h]*azulen-2-ylmethoxy]-ethyl}-amine;*

*dimethyl-[2-(1*H*-8-oxa-1-aza-dibenzo*[e,h]*azulen-2-ylmethoxy)-ethyl]-amine;*

*dimethyl-{3-[1-(2-trimethylsilyl-ethoxymethyl)-1*H*-8-oxa-1-aza-dibenzo*[e,h]*azulen-2-ylmethoxy]-propyl}-amine;*

*dimethyl-[3-(1*H*-8-oxa-1-aza-dibenzo*[e,h]*azulen-2-ylmethoxy)-propyl]-amine;*

*{2-[11-chloro-1-(2-trimethylsilyl-ethoxymethyl)-1*H*-8-oxa-1-aza-dibenzo*[e,h]*azulen-2-ylmethoxy]-ethyl}-dimethyl-amine;*

*[2-(11-chloro-1*H*-8-oxa-1-aza-dibenzo*[e,h]*azulen-2-ylmethoxy)-ethyl]-dimethyl-amine;*

*{3-[11-chloro-1-(2-trimethylsilyl-ethoxymethyl)-1*H*-8-oxa-1-aza-dibenzo*[e,h]*azulen-2-ylmethoxy]-propyl}-dimethyl-amine;*

*[3-(11-chloro-1*H*-8-oxa-1-aza-dibenzo*[e,h]*azulen-2-ylmethoxy)-propyl]-dimethyl-amine;*

*dimethyl-{2-[1-(2-trimethylsilyl-ethoxymethyl)-1*H*-8-thia-1-aza-dibenzo*[e,h]*azulen-2-ylmethoxy]-ethyl}-amine;*

*dimethyl-[2-(1*H*-8-thia-1-aza-dibenzo*[e,h]*azulen-2-ylmethoxy)-ethyl]-amine;*

*dimethyl-{3-[1-(2-trimethylsilyl-ethoxymethyl)-1*H*-8-thia-1-aza-dibenzo*[e,h]*azulen-2-ylmethoxy]-propyl}-amine;*

*dimethyl-[3-(1*H*-8-thia-1-aza-dibenzo*[e,h]*azulen-2-ylmethoxy)-propyl]-amine;*

*3-[1-(2-trimethylsilyl-ethoxymethyl)-1*H*-8-thia-1-aza-dibenzo*[e,h]*azulen-2-ylmethoxy]-propylamine;*

*3-(1*H*-8-thia-1-aza-dibenzo*[e,h]*azulen-2-ylmethoxy)-propylamine.*

ABSTRACT

The present invention relates to the use of compounds from the group of 1-aza-dibenzo[*e,h*]azulenes and of their pharmacologically acceptable salts and solvates for the manufacture of a pharmaceutical formulation for the treatment and prevention of diseases, damages and disorders of the central nervous system (CNS) caused by disorders of the neurochemical equilibrium of biogenic amines.